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(54) Title: METHODS AND COMPOSITIONS FOR TREATING ORAL AND EOSOPHAGEAL LESIONS

(57) Abstract: The invention features methods and compositions for treating or preventing lesions of the upper elimentary canal, particularly oral aphthous or mucositis lesions. Intestinal trefoil peptides are administered in effeective concentrations either alone or in combination with different therapeutic agents.

METHODS AND COMPOSITIONS FOR TREATING ORAL AND ESOPHAGEAL LESIONS

Field of the Invention

This invention provides methods and compositions for treating lesions of the upper alimentary canal including the oral cavity and esophagus.

Background of the Invention

Oral mucositis is the destruction of the oral mucosal epithelium which results in erythema, ulcerations, and pain in the oral cavity. Mucositis often arises as a complication of antineoplastic therapy such as cancer chemotherapy or radiotherapy. The painful ulcerative lesions of mucositis can cause patients to restrict their oral intake of food and liquids; as a result, they lose weight and suffer from dehydration. Severe mucositis can necessitate the de-escalation or the complete interruption of anti-neoplastic therapy. Chemotherapy or radiotherapy can also disrupt mucosal epithelium more distally in the gastrointestinal tract including the esophagus, stomach, and small and large intestines, resulting in pain and organ dysfunction (i.e., diarrhea).

The mucositis lesions are also sites of secondary infections, acting as portals of entry for endogenous oral microorganisms; a particularly serious concern in patients who are immunocompromised. Mucositis is therefore a significant risk factor for chronic debilitating local infections (e.g. yeast (*Candida*) infections) as well as life-threatening systemic infection (septicemia). Patients with mucositis and neutropenia have a relative risk of septicemia that is at least four times greater than that of individuals without mucositis.

Aphthous ulcers of the mouth (or aphthous stomatitis) are a common and painful problem; approximately 10% of the population suffers from these mouth sores at one time or another. The cause of outbreaks of aphthous sores are not

well understood, although they tend to be associated with stress and minor injury to the inside of the mouth. No satisfactory treatments are available, although topical application of steroids provides relief for some patients.

Summary of the Invention

This invention features a method for treating a lesion of the upper alimentary canal in a mammal by administering to the mammal a therapeutically effect amount of an intestinal trefoil peptide. Preferably, the mammal is a human. In preferred embodiments, the intestinal trefoil peptide is spasmolytic polypeptide (SP), pS2, or intestinal trefoil factor (ITF). More preferably, the intestinal trefoil peptide is ITF.

Lesions of the upper alimentary canal such as mucositis, aphthous stomatitis, and gingivitis can be treated by the methods of this invention. Additionally, lesions of the upper alimentary canal that result from antineoplastic therapy (i.e., chemotherapy or radiotherapy), Behcet's Disease, biopsy, surgery, tumor resection, thermal or chemical burns, tooth extraction, trauma from any cause, or lesions caused by microbial (i.e., bacterial, viral, or fungal) infection are also amenable to treatment.

In preferred embodiments, the patient is also administered a second therapeutic agent. Preferred second therapeutic agents include anti-inflammatory agents, antibacterial agents (i.e., penicillins, cephalosporins, tetracyclines, or aminoglycosides), antifungal agents (i.e., nystatin or amphotericin B), antiviral agents (i.e., acyclovir), topical antiseptics (i.e., povidone-iodine), analgesics (i.e., lidocaine or benzocaine), or steroids (i.e., triamcinolone or hydrocortisone). Preferably, the second therapeutic agent is administered within 3 days, 1 day, 12 hours, 1 hour, or simultaneously with the intestinal trefoil peptide. The second therapeutic agent can be present in the same pharmaceutical composition as the intestinal trefoil peptide.

The invention also features pharmaceutical compositions suitable for delivering an intestinal trefoil peptide to the upper alimentary canal. Preferably, the pharmaceutical composition is an oral spray, an oral rinse (mouthwash), an ointment, a paste, a cream, a gel, chewing gum, a chewable tablet, a lozenge, or a bioerodable film. In one embodiment, the pharmaceutical compositions use bioerodable microspheres to encapsulate one or more of the therapeutic agents. In preferred embodiments of an oral spray, rinse, ointment, paste, gel, or bioerodable film, a mucoadhesive or viscosity-enhancing agent is present.

In other preferred embodiments, the intestinal trefoil peptide of the pharmaceutical composition is SP, pS2, or ITF. More preferably, the intestinal trefoil peptide is ITF. In other preferred embodiments, the pharmaceutical composition further contains a second therapeutic. Preferred second therapeutic agents include anti-inflammatory agents, antibacterial agents (i.e., penicillins, cephalosporins, tetracyclines, or aminoglycosides), antifungal agents (i.e., nystatin or amphotericin B), antiviral agents (i.e., acyclovir), topical antiseptics (i.e., povidone-iodine), analgesics (i.e., lidocaine or benzocaine), or steroids (i.e., triamcinolone or hydrocortisone).

By "intestinal trefoil peptide" is meant all mammalian homologs of human spasmolytic polypeptide (SP; also known as TFF2), human pS2 (also known as TFF1) and human intestinal trefoil factor (ITF; also known as TFF3), and biologically active fragments thereof. Homologs of the trefoil peptides have, preferably, 70% amino acid identity to the human sequence, more preferably 85% identity, most preferably 95%, or even 99% sequence identity. The length of comparison sequences will generally be at least about 10 amino acid residues, usually at least 20 amino acid residues, more usually at least 30 amino acid residues, typically at least 45 amino acid residues, and preferably more than 60 amino acid residues.

The term "fragment" is meant to include polypeptides that are truncations or deletions of SP, pS2 and ITF. Preferably, the fragments have 70% amino acid identity to the corresponding regions of the human polypeptide sequence. More

preferably, the fragments are 85% identical, most preferably 95%, or even 99% identical to the human polypeptide sequence to which they correspond. The length of comparison sequences will generally be at least about 10 amino acid residues, usually at least 20 amino acid residues, more usually at least 30 amino acid residues, typically at least 45 amino acid residues, and preferably more than 60 amino acid residues.

Preferable fragments contain four cysteine residues in any positions which correspond to the cysteines at positions 25, 35, 45, 50, 51, 62, or 71, of human ITF (Figure 1), or positions 31, 41, 51, 56, 57, 68, and 82 of human pS2 (Figure 2). More preferably, fragments contain five cysteine residues at these positions. Most preferably, six, or even all seven cysteines are present.

Fragments of SP are meant to include truncations or deletions and preferably have 70% sequence identity to the corresponding human SP polypeptide sequence (Figure 3). More preferably, the fragments are 85% identical, most preferably 95%, or even 99% identical to the human polypeptide sequence. Preferably, active fragments contain at least four cysteine residues which correspond to positions 6, 8, 19, 29, 34, 35, 46, 58, 68, 78, 83, 84, 95, and 104 in the human SP polypeptide. More preferably, fragments contain six cysteines which correspond to these positions. Even more preferable are fragments that contain eight cysteines. Most preferable are fragments that contain cysteines at ten, twelve, or even, all fourteen positions.

It is recognized in the art that one function of the identified cysteine residues is to impart the characteristic three-loop (trefoil) structure to the protein. Accordingly, preferred fragments of ITF and pS2 have a least one loop structure, more preferably, the fragments have two loop structures, and most preferably, they have three loop structures. It is equally well recognized that the native SP polypeptide has a six loop confirmation. Preferable fragments contain at least two of these loop structures, more preferably, four loop structures are conserved, and most preferably, five, or even all six loop structures are present.

By "co-formulated" is meant any single pharmaceutical composition which contains two or more therapeutic or biologically active agents.

By "pharmaceutical preparation" or "pharmaceutical composition" is meant any composition which contains at least one therapeutically or biologically active agent and is suitable for administration to a patient. For the purposes of this invention, pharmaceutical compositions suitable for delivering a therapeutic to the upper alimentary canal include, but are not limited to solutions and suspensions delivered either as an oral spray or rinse, pastes, gels, chewable tablets, sublingual, gingival, or buccal wafers and films, chewing gum, lozenges, and other compositions designed to be retained in the mouth for an extended period of time. Any of these formulations can be prepared by well known and accepted methods of art. See, for example, Remingtion: The Science and Practice of Pharmacy, 19th edition, (ed. AR Gennaro), Mack Publishing Co., Easton, PA, 1995.

By "microsphere" is meant a bioerodable polymeric pharmaceutical delivery device having a diameter of 5-100 μm and a hollow central core suitable for encapsulation of the therapeutic agent. Typically, the therapeutic agent is encapsulated at the time of microsphere formulation.

By "therapeutically effective amount" is meant an amount sufficient to provide medical benefit. When administering trefoil peptides to a human patient according to the methods described herein, a therapeutically effective amount is usually about 0.1-1000 mg of intestinal trefoil peptide per day. Preferably, the patient receives, 10 mg, 100 mg, 250 mg, or 750 mg of intestinal trefoil peptide each day. The total daily does can be divided into multiple individual doses.

By "upper alimentary canal" is meant the portion of the digestive system proximal to the cardiac sphincter (cardioesophageal sphincter) of the stomach. Specifically, the upper alimentary canal is meant to include the oral cavity and associated structures (e.g., the tongue, gingival and sublingual tissues, and the hard and soft palates) and the esophagus.

By "biologically active," when referring to an intestinal trefoil peptide, fragment, or homolog is meant any polypeptide that exhibits an activity common to its related, naturally occurring family member, and that the activity is common to the family of naturally occurring intestinal trefoil peptides. An example of a biological activity common to the family of trefoil peptides is the ability to alter gastrointestinal motility in a mammal.

By "isolated DNA" is meant DNA that is free of the genes which, in the naturally-occurring genome of the organism from which the given DNA is derived, flank the DNA. Thus, the term "isolated DNA" encompasses, for example, cDNA, cloned genomic DNA, and synthetic DNA.

By "treating" is meant administering a pharmaceutical composition for prophylactic and/or therapeutic purposes. The active ingredients of the pharmaceutical composition can treat the primary indication (i.e., epithelial lesion) or secondary symptoms (e.g., concomitant infection, pain, or inflammation).

By "analgesic" is meant an agent which relieves pain by elevating the pain threshold without significantly disturbing the consciousness of the patient.

By "antimicrobial agent" is meant any compound that alters the growth of bacteria or fungi cells, or viruses whereby growth is prevented, stabilized, or inhibited, or wherein the microbes are killed. In other words, the antimicrobial agents can be microbiocidal or microbiostatic.

By "thermal burn" is meant injury to or destruction of at least the epithelial cell layer caused by exposure to excessive temperature. Thermal burns of the upper alimentary canal are usually caused by ingestion of overly-heated foods and liquids, or inhalation of super-heated air. Thermal burns are meant to include, but are not limited to, burns classified as first degree, second degree, and third degree burns.

By "chemical burn" is meant injury to or destruction of at least the epithelial cell layer caused by exposure to noxious chemicals. Typically, chemical exposures of the upper alimentary canal are caused by inhalation or

ingestion.

By "antineoplastic therapy" is meant any treatment regimen used to treat cancer. Typical antineoplastic therapies include chemotherapy and radiation therapy.

Brief Description of Drawings

Figure 1 is the amino acid sequence of a human intestinal trefoil factor (ITF; Accession No. BAA95531; SEQ ID NO: 1).

Figure 2 is the amino acid sequence of a human pS2 protein (Accession No. NP_003216; SEQ ID NO: 2).

Figure 3 is the amino acid sequence of human spasmolytic polypeptide (SP; Accession No. 1909187A; SEQ ID NO:3).

Figure 4 is a cDNA sequence encoding a human intestinal trefoil factor (SEQ ID NO: 4).

Figure 5 is a cDNA sequence encoding a human pS2 protein (SEQ ID NO: 5).

Figure 6 is a cDNA sequence encoding a human spasmolytic polypeptide (SEQ ID NO: 6).

Figure 7 is the nucleotide sequence of a gene encoding human intestinal trefoil factor (locus 10280533:52117-55412; SEQ ID NO: 7).

Figure 8 is the nucleotide sequence of a gene encoding human pS2 protein (locus 10280533:16511-21132; SEQ ID NO: 8).

Figure 9 is the nucleotide sequence of a gene encoding human spasmolytic polypeptide (locus 10280533:957-5208; SEQ ID NO: 9).

Detailed Description

The invention provides methods and compositions useful for the treatment of a wide range of lesions of the upper alimentary canal. The intestinal trefoil peptide therapy of this invention is particularly useful for treating epithelial lesions of the oral and esophageal mucosa, tongue, and gingival tissue.

Mammalian trefoil peptides were discovered in 1982. One of the mammalian trefoil peptides, human intestinal trefoil factor (ITF; TFF3), has been characterized extensively, and is described in U.S. Patent Nos. 6,063,755, and 6,221,840, hereby incorporated by reference. The other two known human intestinal trefoil peptides are spasmolytic polypeptide (SP; TFF2) and pS2 (TFF1). Trefoil peptides, described extensively in the literature (e.g., Sands *et al.*, Annu. Rev. Physiol. 58: 253-273 (1996), hereby incorporated by reference), are expressed in the gastrointestinal tract and have a three-loop structure formed by intrachain disulfide bonds between conserved cysteine residues. These peptides protect the intestinal tract from injury and can be used to treat intestinal tract disorders such as peptic ulcers and inflammatory bowel disease. Homologs of these human peptides have been found in a number of non-human animal species. All members of this protein family, both human and non-human, are referred to herein as trefoil peptides. Human ITF will be referred to most extensively in this application; however, the activity of human ITF is common to each of the mammalian intestinal trefoil peptides.

We have discovered that epithelial lesions of the upper alimentary canal including the oral and esophageal mucosa, tongue, and gingival tissue can be treated by local administration of intestinal trefoil peptides. Thus, trefoil peptide therapy, according to the methods of this invention, can be delivered in any pharmaceutical composition which is useful for delivering therapeutics to the upper alimentary canal.

Pharmaceutical Preparations

Oral Sprays, Rinses, and Emulsions

Spray systems are particularly useful for delivering therapeutics to the upper alimentary canal. Suitable spray delivery systems include both pressurized and non-pressurized (pump actuated) delivery devices. The intestinal trefoil peptide-containing solution, delivered as an oral spray, is preferably an aqueous solution; however, organic and inorganic components, emulsifiers, excipients, and

agents that enhance the organoleptic properties (i.e., flavoring agents or odorants) may be included. Optionally, the solution may contain a preservative that prevents microbial growth (i.e., methyl paraben). Although water itself may make up the entire carrier, typical liquid spray formulations contain a co-solvent, for example, propylene glycol, corn syrup, glycerin, sorbitol solution and the like, to assist solubilization and incorporation of water-insoluble ingredients. In general, therefore, the compositions of this invention preferably contain from about 1-95% v/v and, most preferably, about 5-50% v/v, of the co-solvent. When prepared as an spray, patients typically self-administer 1-5 times per day. The spray delivery system is normally designed to deliver 50-100 µl per actuation, and therapy may require 1-5 actuations per dose. The rheological properties of the spray formulation are optimized to allow shear and atomization for droplet formation. Additionally, the spray delivery device is designed to create a droplet size which promotes retention on mucosal surfaces of the upper alimentary canal and minimize respiratory exposure.

Compositions suitable for oral sprays can also be formulated as an oral rinse or mouthwash. Administration of trefoil peptides using these formulations is typically done by swishing, gargling, or rinsing the oral cavity with the formulation. Optionally, these formulations can be swallowed, providing trefoil peptide therapy to the esophagus, stomach, and/or intestines. This delivery method is particularly useful for treating patients suffering related disorders of the intestinal epithelium. For example, patients receiving antineoplastic chemotherapy, in addition to oral mucositis, frequently develop more distal lesions of the gastrointestinal tract such as lesions of the gastric and intestinal epithelium. It is well known that intestinal trefoil peptides, particularly ITF, are stable at stomach pH. Thus, swallowing an intestinal trefoil peptide-containing solution designed primarily for treating oral mucositis may also benefit lesions of the lower alimentary canal (i.e., stomach and intestines).

In an alternative formulation, the intestinal trefoil peptides and/or other therapeutics can be encapsulated in bioerodable microspheres rather than being dissolved in the aqueous phase of the formulation. A wide variety of microencapsulation drug delivery systems have been developed and many share similar polymeric compositions as used for bioerodable films (described below). Polymers commonly used in the formation of microspheres include, for example, poly-ε-caprolactone, poly(ε-caprolactone-Co-DL-lactic acid), poly(DL-lactic acid), poly(DL-lactic acid-Co-glycolic acid) and poly(ε-caprolactone-Co-glycolic acid) (see, for example, Pitt *et al.*, J. Pharm. Sci., 68:1534, 1979).

Microspheres can be made by procedures well known in the art including spray drying, coacervation, and emulsification (see for example Davis *et al.* Microsphere and Drug Therapy, Elsevier, 1984; Benoit *et al.* Biodegradable Microspheres: Advances in Production Technologies, Chapter 3, Ed. Benita, S, Dekker, New York, 1996; Microencapsulation and Related Drug Processes, Ed. Deasy, Dekker, 1984, New York; U.S. Patent No. 6,365,187). Preferably, the microspheres are bioadhesive or are prepared in formulations containing a bioadhesive excipient.

Other technical features of the intestinal trefoil peptide-containing solutions are easily modified to suit the specific pharmaceutical formulation and the clinical indication being treated. For example, the pH and osmolality of the formulation may be adjusted to confer trefoil peptide stability, while minimizing oral irritancy and sensitivity.

Ointments, Pastes, and Gels

Lesions of the oral and esophageal epithelium caused by trauma are amenable to trefoil peptide therapy delivered as an ointment, paste, or gel. The viscous nature of these types of preparations allows for direct application into the wound site. Optionally, the wound site can be covered with a dressing to retain the trefoil peptide-containing composition, protect the lesion from trauma, and/or absorb exudate. As discussed further below, these preparations are particularly

useful to restore epithelial integrity following traumatic surgical procedures such as, for example, tooth extraction, tissue biopsy, or a tumor resection. Such viscous formulations may also have a local barrier effect thereby reducing irritation and pain.

Mucoadhesives

A mucoadhesive excipient can be added to any of the previously described pharmaceutical compositions. The mucoadhesive formulations coat the upper alimentary canal providing protection, inhibiting irritation, and accelerating healing of inflamed or damaged tissue. Mucoadhesive formulations also promote prolonged contact of the intestinal trefoil peptide with the mucosal epithelium. Mucoadhesive formulations suitable for use in pharmaceutical preparations delivered by mouth are well known in the art (e.g., U.S. Patent No. 5,458,879). Particularly useful mucoadhesives are hydrogels composed of about 0.05-20% of a water-soluble polymer such as, for example, poly(ethylene oxide), poly(ethylene glycol), poly(vinyl alcohol), poly(vinyl pyrrolidine), poly(acrylic acid), poly(hydroxy ethyl methacrylate), hydroxyethyl ethyl cellulose, hydroxy ethyl cellulose, chitosan, and mixtures thereof. These polymeric formulations can also contain a dispersant such as sodium carboxymethyl cellulose (0.5-5.0%).

Other preferred mucoadhesive excipients for liquid compositions are ones that allow the composition to be administered as a flowable liquid but will cause the composition to gel in the upper alimentary canal, thereby providing a bioadhesive effect which acts to hold the therapeutic agents at the lesion site for an extended period of time. The anionic polysaccharides pectin and gellan are examples of materials which when formulated into a suitable composition will gel in the upper alimentary canal, owing to the presence of cations in the mucosal and salivary fluids. The liquid compositions containing pectin or gellan will typically consist of 0.01-20% w/v of the pectin or gellan in water or an aqueous buffer system.

Other useful compositions which promote mucoadhesion and prolonged therapeutic retention in the upper alimentary canal are colloidal dispersions containing 2-50% colloidal particles such as silica or titanium dioxide. Such formulations form as a flowable liquid with low viscosity suitable as a mouthwash or for generating a fine mist. However, the particles interact with glycoprotein, especially mucin, transforming the liquid into a viscous gel, providing effective mucoadhesion (e.g., U.S. Patent Nos. 5,993,846 and 6,319,513).

Bioerodable Film Delivery Devices

The most simple bioerodable devices contain the therapeutic agent(s) incorporated into a solid, usually lipid-containing, film or tablet. The device is formulated to remain solid at room temperature, but melt at body temperature, releasing the incorporated therapeutics. Suitable formulations of this type include, for example, cocoa butter.

Polymeric film devices provide several advantages for therapeutic delivery to the oral cavity. Unlike rinses, pastes, gels, and other flowable compositions, a film device can reside for prolonged periods of time (i.e., hours to days) in the oral cavity and provide sustained release throughout its residency. Typically, the film is partially or completely bioerodable and contains a mucoadhesive layer to fasten the film to the oral mucosa. Film devices, in addition to its use for delivering therapeutics, can also provide protection against mechanical injury or microbial infection of a lesion site. This physical barrier function is particularly advantageous when treating conditions such as mucositis or aphthous stomatitis. Additionally, as discussed further below, a film device can be used to release trefoil peptide therapy directly onto the underlying mucosa, into the lumen of the oral cavity, or a combination of both.

Film devices consist of at least two layers; a mucoadhesive layer suitable for attaching the film to the oral mucosa and a bulk layer which contains the active therapeutic(s). Many suitable mucoadhesives are known in the art and are discussed above. Optionally, one or more therapeutics can also be provided in the

adhesive layer.

The bulk layer of the composite delivery device may be made of one or more bioerodable polymeric materials. Suitable polymers include, for example, starch, gelatin, polyethylene glycol, polypropylene glycol, polyethylene oxide, copolymers of ethylene oxide and propylene oxide, copolymers of polyethylene glycol and polypropylene glycol, polytetramethylene glycol, polyether urethane, hydroxyethyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, alginate, collagen, polylactide, poly(lactide-co-glycolide) (PLGA), calcium polycarbophil, polyethymethacrylate, cellulose acetate, propylene glycol, polyacrylic acid, crosslinked polyacrylic acid, hydroxyethyl methacrylate/methyl methacrylate copolymer, silicon/ethyl cellulose/polyethylene glycol, urethane polyacrylate, polystyrene, polysulfone, polycarbonate, polyorthoesters, polyanhydrides, poly(amino acids), partially and completely hydrolyzed alkylene-vinyl acetate copolymers, polyvinyl chloride, polymers of polyvinyl acetate, polyvinyl alkyl ethers, styrene acrylonitrile copolymers, poly(ethylene terphthalate), polyalkylenes, poly(vinyl imidazole), polyesters and combinations of two or more of these polymers.

A particularly useful bulk layer polymer consists of PLGA and ethyl cellulose. PLGA is bioerodable and can be formulated to degrade over a wide range of conditions and rates. Ethyl cellulose is a water-insoluble polymer that can act as a plasticizer for the PLGA when a film is formed, but will be eroded in a bodily fluid. Due to its water-insolubility, it also has an effect on the degree and rate of swelling of the resultant film.

An optional third layer which is impermeable to the trefoil peptide can also be added to the wafer. Preferably, this barrier layer is also bioerodable. Suitable barrier layer polymers include ethyl cellulose, poly(acrylic acid), or other polyelectrolytes. In one configuration, the barrier layer is placed on the opposite side of the bulk layer relative to the adhesive layer, thereby directing the released therapeutic agent onto the contacted epithelium rather than being diluted in the lumenal fluid. This configuration is particularly useful for treating discrete

lesions (i.e., mucositis or aphthous stomatitis) of the tongue, sublingual tissue, or buccal mucosa. In an alternative configuration of the film device, the barrier layer is placed between the bulk layer and the adhesive layer. This configuration directs therapeutic release into the lumen of the oral cavity and is useful for treating more diffuse lesions of the tongue, oral cavity, and esophagus. The configuration is also useful for delivering therapeutics which are cytotoxic when administered at high concentrations because it has the effect of shielding the underlying tissue from direct contact with the therapeutic-containing film.

Chewable Tablets, Lozenges, and Confectionaries

Preparing a trefoil peptide-containing composition as a chewable tablet, lozenge, or a confectionary such as chewing gum provides several advantages to traditional drug delivery vehicles. First, prolonged contact and sustained release at the target site (mouth and esophagus) is achieved. Second, such formulations often results in higher patient compliance, especially when administering trefoil peptides to children.

Formulations for chewable tablets are well known and typically contain a base of sugar, starch, or lipid and a flavoring agent. An exemplary formulation for a chewable tablet is provided below.

Chewable ITF Tablet Formulation (per tablet)

Intestinal trefoil factor – 300 mg
Mannitol – 675 mg
Microcrystalline cellulose – 75mg
Corn starch – 30 mg
Calcium sterate – 22 mg
Flavoring Agent (i.e., sodium saccharin or peppermint oil)

The incorporation of therapeutics into chewing gum and other confectionary style formulations is known in the art (e.g., U.S. Patent No. 5,858,391).

Therapeutics Agents

Trefoil Peptides

In preferred embodiments, the trefoil peptide is a human trefoil peptide. More preferably, it is human intestinal trefoil factor (ITF), spasmolytic polypeptide (SP), or pS2. Most preferably, the trefoil peptide is human ITF.

The trefoil peptides are present in the compositions of the invention at a concentration of between 0.1-1000 mg/ml, depending on the nature and condition of the lesion being treated, the anticipated frequency and duration of therapy, and the type of pharmaceutical composition used to deliver the trefoil peptide. Typically, therapy is designed to deliver 0.1-500 mg of trefoil peptide per day to the patient.

Anti-Inflammatory Agents

Any suitable anti-inflammatory agent can be formulated in the compositions of the invention, at concentrations known for these agents. Many of the most useful anti-inflammatory agents also have analgesic and/or antipyretic properties. Anti-inflammatory agents suitable for co-formulation with a trefoil peptide include, for example, acetaminophen, aspirin (acetylsalicylic acid), ibuprofen, phenylbutazone, indomethacin, sulindac, diclofenac, and naproxen.

Antimicrobial Agents

Any of the many known microbial agents can be used in the compositions of the invention at concentrations generally used for these agents. Antimicrobial agents include antibacterials, antifungals, antivirals, and other topical antiseptics.

Examples of antibacterial agents (antibiotics) include the penicillins (e.g., penicillin G, ampicillin, methicillin, oxacillin, and amoxicillin), the cephalosporins (e.g., cefadroxil, ceforanid, cefotaxime, and ceftriaxone), the tetracyclines (e.g., doxycycline, minocycline, and tetracycline), the aminoglycosides (e.g., amikacin, gentamycin, kanamycin, neomycin, streptomycin, and tobramycin), the macrolides (e.g., azithromycin, clarithromycin,

and erythromycin), the fluoroquinolones (e.g., ciprofloxacin, lomefloxacin, and norfloxacin), and other antibiotics including chloramphenicol, clindamycin, cycloserine, isoniazid, rifampin, and vancomycin.

Antiviral agents are substances capable of destroying or suppressing the replication of viruses. Examples of anti-viral agents include 1,-D-ribofuranosyl-1,2,4-triazole-3 carboxamide, 9->2-hydroxy-ethoxy methylguanine, adamantanamine, 5-iodo-2'-deoxyuridine, trifluorothymidine, interferon, adenine arabinoside, protease inhibitors, thymadine kinase inhibitors, sugar or glycoprotein synthesis inhibitors, structural protein synthesis inhibitors, attachment and adsorption inhibitors, and nucleoside analogues such as acyclovir, penciclovir, valacyclovir, and ganciclovir.

Antifungal agents include both fungicidal and fungistatic agents such as, for example, amphotericin B, butylparaben, clindamycin, econaxole, fluconazole, flucytosine, griseofulvin, nystatin, and ketoconazole.

Topical antiseptics include agents such as, for example, povidone-iodine and benzalkonium chloride.

Analgesics and Anesthetics

Any of the commonly used topical analgesics can be used in the compositions of the invention. The analgesic is present in an amount such that there is provided to the oral lesion a topical concentration of between one-half and five percent concentration for lidocaine (5-50 mg/ml in 20-40 ml per dose of liquid). Examples of other useful anesthetics include procaine, lidocaine, tetracaine, dibucaine, benzocaine, p-buthylaminobenzoic acid 2-(diethylamino) ethyl ester HCl, mepivacaine, piperocaine, and dyclonine.

Other analgesics include opioids such as, for example, morphine, codeine, hydrocodone, and oxycodone. Any of these analgesics may also be co-formulated with other compounds having analgesic or anti-inflammatory properties, such as acetaminophen, aspirin, and ibuprofen.

Steroids

Steroids are commonly used to treat lesions of the upper alimentary canal. For example, oral aphthous stomatitis is typically treated using a paste preparation of triamcinolone (0.1%), hydrocortisone, fluticasone, or beclomethasone.

Conditions of the Upper Alimentary Canal Treated Using Trefoil Peptides

Mucositis

Mucositis is a common condition of the oral cavity which is characterized by inflammation of the mucous membranes. The condition is frequently caused by antineoplastic therapy, including chemotherapy and local radiation therapy. Symptoms of mucositis include ulcerations, redness, and swelling, and is associated with epithelial cell injury and death. Patients suffering from severe mucositis are susceptible to dehydration and malnutrition because mucositis pain limits dietary intake. In severe cases, mucositis can be so debilitating that patients may require prolonged hospitalization, parenteral nutrition, and narcotic pain medication. Additionally, destruction of the mucosal epithelium increases a patient's susceptibility to local and systemic infection. Disruption of the barrier function permits entry of microorganisms and microbial products normally retained in the gut lumen. Thus, pharmaceutical preparations which reduce the adverse effects associated with chemotherapy will improve the patient's quality of life, compliance with self-medication, and may permit administration of higher chemotherapeutic doses. Typically, mucositis is treated using a trefoil peptide-containing rinse or oral spray which the patient self-administers 1-5 times per day. The aqueous solution preferably contains a mucoadhesive and an anti-inflammatory agent. Other therapeutics, such as an topical analgesic agent (e.g., lidocaine) may also be present. Alternatively, if the lesions are few in number and spatially localized, an intestinal trefoil peptide-containing film device an be placed directly over the lesions.

Tooth Extraction

Intestinal trefoil peptide-containing compositions of the invention are used to lessen complications and speed healing of the wound created by the extraction of a tooth. An oral rinse, paste, ointment, or gel, as described above, is applied to the site of extraction immediately following the procedure and then 1-4 times per day, as needed, until epithelial regrowth is complete. Preferably, a topical analgesic is included in the formulation to relieve the temporary discomfort cause by the trauma of extraction. As a prophylactic measure, antibiotic agents may also be included in the formulation.

Gingivitis

Gingivitis is most commonly a chronic disease requiring ongoing treatment, in some cases for months or even years. The trefoil peptide-containing compositions of the invention can be employed to treat gingivitis, alone or in conjunction with other treatments, particularly with an anti-microbial agent, and most commonly with an antibacterial agent. An oral intestinal trefoil peptide-containing rinse is swished in the patient's mouth at least once every 2-3 days, but as often as thrice daily, over a 3-4 week period, and the regimen is repeated as needed. Alternatively, the trefoil peptide is formulated into a gel or toothpaste. In severe cases, a viscous gel or ointment having a high intestinal trefoil peptide concentration is applied directly to the wound via a pledget with a stick applicator.

Intestinal trefoil peptide-containing compositions can also be delivered in biodegradable drug delivery systems capable of formation of films applied below the gum line (described in U.S. Patent Nos. 5,945,115 and 5,990,194. A biodegradable polymer, admixed with the intestinal trefoil peptide, is provided where the polymer can be injected in as a free-flowing solution below the gum line using a syringe. The polymer solution then, *in situ,* forms a solid biodegradable implant.

Aphthous Stomatitis

At the first indication of an outbreak of aphthous stomatitis (generally, the first twinge of pain), the patient swishes the mouth with an intestinal trefoil peptide-containing rinse, 1-4 times per day until the ulcer heals (generally 5-10 days). An intestinal trefoil peptide-containing gel can also be applied to the ulcer, in the same manner that steroid-containing gels are currently used. In addition, a gel can contain both an intestinal trefoil protein and a steroid known to be effective for aphthous stomatitis treatment. A direct application of more concentrated material can be directly applied to the wound via a pledget with a stick applicator. Alternatively, the lesion can be treated directly by applying a bioerodable film device containing both a trefoil peptide and a steroid (i.e., triamcinolone) directly to the lesion. Any formulation useful for treating aphthous stomatitis can also, optionally, contain a local anesthetic (i.e., lidocaine or benzocaine).

Behcet's Disease

Behcet's Disease is a rare, multi-system rheumatic disorder characterized by systemic vasculitis. One of the most frequent symptoms of Behcet's Disease is recurrent oral ulcerations which resemble aphthous lesions. Currently, treatment for Behcet's Disease is palliative, not curative. Thus, the intestinal trefoil peptides can be used to treat lesions of the upper alimentary canal in conjunction with currently available Behcet's Disease therapies including, for example, interferon alpha 2A and 2B, levamisole, cyclosporine, cyclophosphamide, and colchicine.

Oral Biopsy and Oral Surgery

In cases in which an oral neoplasm is suspected or known to be malignant, a biopsy or a curative resection is performed using a needle or a scalpel, resulting in an open wound. The surgical area, susceptible to infection and inflammation, is treated by rinsing with a trefoil peptide-containing solution 1-4 times per day.

Preferably, an analgesic, an anti-inflammatory, and an antibiotic are included in the formulation. Alternatively, a more concentrated gel, paste, or ointment may be directly applied to the lesion site. For post-operative treatment following resection of a malignancy, a topically active chemotherapeutic can be including in the trefoil peptide-containing composition.

Thermal and Chemical Burns

Trauma to the upper alimentary canal is frequently caused by exposure to excessive heat or noxious chemicals. Thermal burns to the upper alimentary canal are frequently mild in nature (i.e., first or second degree burns), resulting from the ingestion of overheated food or drink. More severe thermal burns of the oral mucosa and upper esophagus can be caused by inhalation of super heated air and are frequently observed in firefighters or victims of house or forest fires.

Chemical exposure can also damage the mucosa of the upper alimentary canal. Mild mucosal irritations and burns are often caused by ingestion of acidic food (i.e., fruits). More severe chemical burns are usually associated with accidental industrial or occupational exposures.

The intestinal trefoil peptide-containing pharmaceutical formulations described herein are useful for treating thermal and chemical burns of the upper alimentary canal. Preferably, viscous liquid or gel formulation containing a mucoadhesive is used to prolong mucosal exposure to the trefoil peptide. Alternatively, a sustained release formulation, such as a bioerodable film, is used. Topical analgesics and antimicrobial agents are the most preferred secondary therapeutics to be co-administered.

Production of Intestinal Trefoil Peptides

Intestinal trefoil peptides can be produced by any method known in the art for expression of recombinant proteins. Nucleic acids that encode trefoil peptides (e.g., human intestinal trefoil factor (Figure 4 and 7), human pS2 (Figure 5 and 8), and human spasmolytic polypeptide (Figure 6 and 9) or fragments thereof may be

introduced into various cell types or cell-free systems for expression thereby allowing large-scale production, purification, and patient therapy.

Eukaryotic and prokaryotic trefoil peptide expression systems may be generated in which an intestinal trefoil peptide gene sequence is introduced into a plasmid or other vector, which is then used to transform living cells. Constructs in which the intestinal trefoil peptide cDNA contains the entire open reading frame inserted in the correct orientation into an expression plasmid may be used for protein expression. Prokaryotic and eukaryotic expression systems allow for the expression and recovery of intestinal trefoil peptide fusion proteins in which the trefoil peptide is covalently linked to a tag molecule which facilitates identification and/or purification. An enzymatic or chemical cleavage site can be engineered between the trefoil peptide and the tag molecule so that the tag can be removed following purification.

Typical expression vectors contain promoters that direct the synthesis of large amounts of mRNA corresponding to the inserted intestinal trefoil peptide nucleic acid in the plasmid-bearing cells. They may also include a eukaryotic or prokaryotic origin of replication sequence allowing for their autonomous replication within the host organism, sequences that encode genetic traits that allow vector-containing cells to be selected for in the presence of otherwise toxic drugs, and sequences that increase the efficiency with which the synthesized mRNA is translated. Stable long-term vectors may be maintained as freely replicating entities by using regulatory elements of, for example, viruses (e.g., the OriP sequences from the Epstein Barr Virus genome). Cell lines may also be produced that have integrated the vector into the genomic DNA, and in this manner the gene product is produced on a continuous basis.

Expression of foreign sequences in bacteria, such as *Escherichia coli,* requires the insertion of an intestinal trefoil peptide nucleic acid sequence into a bacterial expression vector. Such plasmid vectors contain several elements required for the propagation of the plasmid in bacteria, and for expression of the DNA inserted into the plasmid. Propagation of only plasmid-bearing bacteria is

achieved by introducing, into the plasmid, selectable marker-encoding sequences that allow plasmid-bearing bacteria to grow in the presence of otherwise toxic drugs. The plasmid also contains a transcriptional promoter capable of producing large amounts of mRNA from the cloned gene. Such promoters may be (but are not necessarily) inducible promoters that initiate transcription upon induction. The plasmid also preferably contains a polylinker to simplify insertion of the gene in the correct orientation within the vector. Mammalian cells can also be used to express a trefoil peptide. Stable or transient cell line clones can be made using intestinal trefoil peptide expression vectors to produce the trefoil peptides in a soluble (truncated and tagged) form. Appropriate cell lines include, for example, COS, HEK293T, CHO, or NIH cell lines.

Once the appropriate expression vectors are constructed, they are introduced into an appropriate host cell by transformation techniques, such as, but not limited to, calcium phosphate transfection, DEAE-dextran transfection, electroporation, microinjection, protoplast fusion, or liposome-mediated transfection. The host cells that are transfected with the vectors of this invention may include (but are not limited to) *E. coli* or other bacteria, yeast, fungi, insect cells (using, for example, baculoviral vectors for expression in SF9 insect cells), or cells derived from mice, humans, or other animals. *In vitro* expression of trefoil peptides, fusions, or polypeptide fragments encoded by cloned DNA may also be used. Those skilled in the art of molecular biology will understand that a wide variety of expression systems and purification systems may be used to produce recombinant trefoil peptides and fragments thereof. Some of these systems are described, for example, in Ausubel *et al.* (Current Protocols in Molecular Biology, John Wiley & Sons, New York, NY 2000, hereby incorporated by reference).

Transgenic plants, plant cells and algae are also particularly useful for generating recombinant intestinal trefoil peptides for use in the methods and compositions of the invention. For example, transgenic tobacco plants or cultured transgenic tobacco plant cells expressing an intestinal trefoil peptide can be

created using techniques known in the art (see, for example, U.S. Patent Nos. 5,202,422 and 6,140,075). Transgenic algae expression systems can also be used to produce recombinant intestinal trefoil peptides (see, for example, Chen et al., Curr. Genet. 39:365-370, 2001).

Once a recombinant protein is expressed, it can be isolated from cell lysates using protein purification techniques such as affinity chromatography. Once isolated, the recombinant protein can, if desired, be purified further by e.g., high performance liquid chromatography (HPLC; e.g., see Fisher, Laboratory Techniques In Biochemistry And Molecular Biology, Work and Burdon, Eds., Elsevier, 1980).

Polypeptides of the invention, particularly short intestinal trefoil peptide fragments can also be produced by chemical synthesis using, for example, Merrifield solid phase synthesis, solution phase synthesis, or a combination of both (see, for example, the methods described in Solid Phase Peptide Synthesis, 2nd ed., 1984, The Pierce Chemical Co., Rockford, IL). Optionally, peptide fragments are then be condensed by standard peptide assembly chemistry.

Example 1: Mucositis Treatment for Patients Receiving Antineoplastic Therapy

Trefoil peptide therapy is initiated prior to antineoplastic therapy (i.e., chemotherapy or radiation therapy), as a prophylactic to delay or prevent the onset of mucositis. Preferably, the patient begins intestinal trefoil peptide therapy three days prior to the first dose of antineoplastic therapy. During the prophylactic stage, the patient rinses the oral cavity with an intestinal trefoil peptide-containing solution. Alternatively, for convenience, the trefoil peptide is provided as a concentrated oral spray. Preferably, the patient swallows the solution, providing protection for the epithelial cells of the esophagus and lower gastrointestinal tract. Rinsing with and swallowing the intestinal trefoil peptide-containing solution continues at least twice daily until oral or esophageal mucositis is detected.

In patients with existing mucositis, epithelial healing is promoted using intestinal trefoil peptide therapy as described above. Palliative therapy is provided using benzocaine (a local anesthetic), and nystatin (an antifungal). The intestinal trefoil peptide can be co-formulated with the benzocaine and nystatin. For example, the patient swishes an oral rinse solution (mouthwash), containing all therapeutic agents, 1-5 times each day. Alternatively, the trefoil peptide can be provided in a concentrated oral spray, with or without benzocaine and the nystatin is administered in an oral rinse.

The oral rinse solutions can either be swallowed or spit out. If swallowed, an antacid may also be included in the formulation. Other useful therapeutics which provide palliative therapy include anti-inflammatories (e.g., ibuprofen) and other anti-microbial agents. Exemplary oral rinses useful for treating chemotherapy-induced mucositis are provided below, but are not intended to be limiting. A skilled physician or pharmacist will immediately recognize appropriate substitutions, additions, and deletions that can be made to these formulations.

Rinse#1: Mix equal parts of:

(i) diphenhydramine elixir (Benadryl®)

(ii) kaolin-pectin suspension (Kaopectate®)

(iii) viscous lidocaine HCl (2%)

(iv) nystatin (oral suspension; 100,000 iu/ml)

(v) ITF (2.5 mg/ml)

preferably swallowed after swishing

Rinse#2: Mix equal parts of:

(i) diphenhydramine elixir (Benadryl®)

(ii) Maalox® (MgOH & AlOH; 40 mg/ml)

(iii) viscous lidocaine HCl (2%)

(iv) ITF (2.5 mg/ml)

preferably swallowed after swishing

Other Embodiments

All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

What is claimed is:

CLAIMS

1. A method for treating a lesion of the upper alimentary canal of a mammal comprising administering to said patient a therapeutically effective amount of an intestinal trefoil peptide.

2. The method of claim 1, wherein said intestinal trefoil peptide is spasmolytic polypeptide, pS2, or intestinal trefoil factor.

3. The method of claim 2, wherein said intestinal trefoil peptide is intestinal trefoil factor.

4. The method of claim 1, wherein said mammal is a human.

5. The method of claim 1, wherein said lesion is mucositis.

6. The method of claim 1, wherein said lesion is aphthous stomatitis.

7. The method of claim 1, wherein said lesion is caused by antineoplastic therapy.

8. The method of claim 7, wherein said antineoplastic therapy is radiation therapy.

9. The method of claim 7, wherein said antineoplastic therapy is chemotherapy.

10. The method of claim 1, wherein said lesion is the result of gingivitis.

11. The method of claim 1, wherein said lesion is the result of tooth extraction.

12. The method of claim 1, wherein said lesion is the result of a biopsy procedure or surgical intervention.

13. The method of claim 1, wherein said lesion is the result of tumor resection.

14. The method of claim 1, wherein said lesion is caused by thermal or chemical burn.

15. The method of claim 1, wherein said lesion is caused by Behcet's Disease.

16. The method of claim 1, wherein said lesion is caused by a bacterial, viral, or fungal infection.

17. The method of claim 1, further comprising administering to said mammal a second therapeutic.

18. The method of claim 17, wherein said second therapeutic agent is an anti-inflammatory agent.

19. The method of claim 17, wherein said second therapeutic agent is an antibacterial agent.

20. The method of claim 19, wherein said antibacterial agent is a penicillin, a cephalosporin, a tetracycline, or an aminoglycoside.

21. The method of claim 19, wherein said antibacterial agent is povidone-iodine.

22. The method of claim 17, wherein said second therapeutic agent is an anti-fungal agent.

23. The method of claim 22, wherein said anti-fungal agent is nystatin or Amphotericin B.

24. The method of claim 17, wherein said second therapeutic agent is an anti-viral agent.

25. The method of claim 24, wherein said anti-viral agent is acyclovir.

26. The method of claim 17, wherein said second therapeutic agent is an analgesic.

27. The method of claim 26, wherein said analgesic is lidocaine or benzocaine.

28. The method of claim 17, wherein said second therapeutic agent is a steroid.

29. The method of claim 28, wherein said steroid is triamcinolone or hydrocortisone.

30. The method of claim 17, wherein said trefoil peptide and said second therapeutic are administered in the same formulation.

31. The method of claim 17, wherein said trefoil peptide and said second therapeutic are administered in different formulations.

32. The method of claim 31, wherein said trefoil peptide and said second therapeutic are administered within 24 hours of each other.

33. The method of claim 32, wherein said trefoil peptide and said second therapeutic are administered within one hour of each other.

34. A composition suitable for therapeutic delivery to the upper alimentary canal of a mamml, said composition comprising an intestinal trefoil peptide.

35. The composition of claim 34, wherein said intestinal trefoil peptide is spasmolytic polypeptide, pS2, or intestinal trefoil factor.

36. The composition of claim 35, wherein said intestinal trefoil peptide is intestinal trefoil factor.

37. The composition of claim 34, wherein said composition is an oral spray.

38. The composition of claim 34, wherein said composition is an oral rinse.

39. The composition of claim 34, wherein said composition is a bioerodable film.

40. The composition of claim 34, wherein said composition comprises microspheres.

41. The composition of claim 37, 38, 39, or 40, wherein said composition further comprises a mucoadhesive agent.

42. The composition of claim 34, wherein said composition is a chewing gum, lozenge, or chewable tablet.

43. The composition of claim 34, wherein said composition further comprises a second therapeutic agent.

44. The composition of claim 43, wherein said second therapeutic agent is an anti-inflammatory agent.

45. The composition of claim 43, wherein said second therapeutic agent is an antibacterial agent.

46. The composition of claim 45, wherein said antibacterial agent is a penicillin, a cephalosporin, a tetracycline, or an aminoglycoside.

47. The composition of claim 45, wherein said antibacterial agent is povidone-iodine.

48. The composition of claim 43, wherein said second therapeutic agent is an anti-fungal agent.

49. The composition of claim 48, wherein said anti-fungal agent is nystatin or Amphotericin B.

50. The composition of claim 43, wherein said second therapeutic agent is an anti-viral agent.

51. The composition of claim 50, wherein said anti-viral agent is acyclovir.

52. The composition of claim 43, wherein said second therapeutic agent is an analgesic.

53. The composition of claim 52, wherein said analgesic is lidocaine or benzocaine.

54. The composition of claim 43, wherein said second therapeutic agent is a steroid.

55. The composition of claim 54, wherein said steroid is triamcinolone or hydrocortisone.

FIGURE 1

1 MLGLVLALLS SSSAEEYVGL SANQCAVPAK DRVDCGYPHV
41 TPKECNNRGC CFDSRIPGVP WCFKPLQEAE CTF

FIGURE 2

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1   MATMENKVIC ALVLVSMLAL GTLAEAQTET CTVAPRERQN
41  CGFPGVTPSQ CANKGCCFDD TVRGVPWCFY PNTIDVPPEE
81  ECEF
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FIGURE 3

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1   EKPSPCQCSR LSPHNRTNCG FPGITSDQCF DNGCCFDSSV
41  TGVPWCFHPL PKQESDQCVM EVSDRRNCGY PGISPEECAS
81  RKCCFSNFIF EVPWCFFPNS VEDCHY
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FIGURE 4

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1    atgctggggc tggtcctggc cttgctgtcc tccagctctg ctgaggagta cgtgggcctg
61   tctgcaaacc agtgtgccgt gccagccaag gacagggtgg actgcggcta cccccatgtc
121  acccccaagg agtgcaacaa ccggggctgc tgctttgact ccaggatccc tggagtgcct
181  tggtgtttca agcccctgca ggaagcagaa tgcaccttct ga
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FIGURE 5

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1    atggccacca tggagaacaa ggtgatctgc gccctggtcc tggtgtccat gctggccctc
61   ggcaccctgg ccgaggccca gacagagacg tgtacagtgg ccccccgtga aagacagaat
121  tgtggttttc ctggtgtcac gccctcccag tgtgcaaata agggctgctg tttcgacgac
181  accgttcgtg gggtcccctg gtgcttctat cctaatacca tcgacgtccc tccagaagag
241  gagtgtgaat tttag
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FIGURE 6

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1    atgggacggc gagacgccca gctcctggca gcgctcctcg tcctggggct atgtgccctg
61   gcggggagtg agaaaccctc cccctgccag tgctccaggc tgagccccca taacaggacg
121  aactgcggct tccctggaat caccagtgac cagtgttttg acaatggatg ctgtttcgac
181  tccagtgtca ctggggtccc ctggtgtttc cacccctcc caaagcaaga gtcggatcag
241  tgcgtcatgg aggtctcaga ccgaagaaac tgtggctacc cgggcatcag ccccgaggaa
301  tgcgcctctc ggaagtgctg cttctccaac ttcatctttg aagtgccctg gtgcttcttc
361  ccgaagtctg tggaagactg ccattactaa
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FIGURE 7

(page 1 of 2)

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1    atgctggggc tggtcctggc cttgctgtcc tccagctctg ctgaggagta cgtgggcctg
61   tgtgagtact gccctgactg ccccggtggc agggtgggcg tgaagggaag ggatccagga
121  taaggggggа ttctgcattc atttaataat ggccacctgt cacatataca ctttttcctg
181  cgctagccct ttgaagtggg tctttattgt ccccatttca cagacaagga aaccgaggct
241  cagagaaagt taacaactta tccaaggcag ccctgcccag tctgtgttga aatcagggtt
301  tgagcctgag cccatcccct atgaccccat agccatcttt gctggagatt tctaaattac
361  aatataggtc tttatgcatt gttccacatt tacaaagaaa aaggaaagat gcaggagaaa
421  aaccctgact tcagaacact gtcaataccg gcaggcacaa ggttcattta gccattgcat
481  agcaaccctg ccatggggtg tggctgctcc attaacccaa gtttgaagga atgagggcat
541  ggcttttatc tgggtgtctt ctgagcaggg tcaaaggcag tggttcccga acttgcagcc
601  cattagaatc acctggagag ctttaaaaat cctaatgctt ggggcacacc agttacatca
661  gggcatctcc aggcaagatc caggcctcag ctgttttgtt ttgagatagc cttgctttgt
721  cactcactgc tggagtgcag tggcacaatc tcagctcact gcaacctccg cctcctgggt
781  tcaagcaatt cttgtgcctc ggcttcaagt agctgggatt acaggcatgc accaccatgc
841  ccagctaatt ttttggattt ttagtagaga tggagtttcg ctatgttggc caagctggtc
901  tcaaactcct ggcctcaagt gatcctcctg ccttggcctc ccaaagtgct ggaattacag
961  gtgtaagcca ccatgcccag ccaacgtcag tcatttttaa agctctgcag ctgattccag
1021 tgtgagcgaa gtttggatgc caggaggata agcaattacg gactgggagc aagagaaggg
1081 aatgtaagac actgcacgtg attgccattt tcctaaggaa atactcagtt cgttaatgaa
1141 acgcagtgaa cttctgctgc acatacagac atagaggctt gcctgaaaca tgaaaatatt
1201 ggggactgaa ggatgtcccg ggagggtggg acatgctcaa caattcagga aggggagatg
1261 cagaaaaaag tgaaaagcag gcagcatgcg ttgcaatgat ctctatggcg tgtgcctctc
1321 ctgtcacggt tttcatttaa aacaaagggg caaggttttg ttggtcaaac aatgaagggt
1381 aactttgttt ctgggttcaa gggaccccag attccccagg ggttcctgcc agctggaagg
1441 tacccaggtc cgtatgtgac ttcccgagaa ggtgataaga gcgtgccaag gagaaagaca
1501 cttaggcaaa tggccagagt ccccgagctg agcatttaac agactgcctc tctttaaata
1561 ttcacaggga aagtgcatct tcctaagggc gagggtttca gcagtggttg aactcggcgg
1621 ggtggggcgg agcgggagga tgcaaacttg caaagtgaag caaacacact caccgcagcc
1681 cagcaagggc tctggcagct gacagggctt tgtctgggac agctgcaaac cagtgtgccg
1741 tgccagccaa ggacagggtg gactgcggct acccccatgt caccccccaag gagtgcaaca
1801 accggggctg ctgctttgac tccaggatcc ctggagtgcc ttggtgtttc aagcccctgc
1861 aggaagcagg taaggcccca gtggcatcgt ggtctgggcc cagccccata aggcaggggg
1921 tctcagggcc tccctgtcct ttctgggctg gagatggagg cacaaggacc ccaggaagcc
1981 acacacacac acctgttcca aggcctcaga gcagaggctt cacacttagg gcagccatgg
2041 ccaggggctg tcctcttctg tcccctttat gtaaaacata aaagcaattg tttcaaaaag
2101 gtgttcaaaa tgatggcatc gcatagaggg aactgattta gtaactattc ttgagagaag
2161 tggaaacgca taggtgtgga aagccgggcc gacttttggg ctgtttttgc aaatcggccc
2221 cccagagtct tgtcatttgt ggcatcccct acacagacgg caggcggtcc cagccctaga
2281 cgtcaggcct cggtgccaca ccccacctcc cccactctgc cccccacaag ggtcatctcc
2341 tctccctctc tctgccgtgg tggagggcag gtgcagggca accaccctgg gggttccctc
2401 cccaggggcg gagagcctgc gtgctgtgcg ggtaacagat ggccctgcac acgggtttgc
2461 caccctggct ccaccaggct tagctgcccc acatcgtggg tggggcgatt ggctataagc
2521 catctgccat gtccaagtgc cagctcagcc cccacgaagg ccgcacctgc gtgaggtacc
2581 ttcctggaac cagcatccag aggggcctct cttgcccttt gtcctagggt gaaatgcggg
2641 aggctgagtc ctgctggccc cggctccctg atcaatgatg ggcccctgcc cagggcctcc
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FIGURE 7

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2701 cttcaccctc cccagcaagt ccagggtagg ggtgggggtg ggggtccaga gaaggccagg
2761 agagagaggg gtctggctac tgtccactgc cggtcctgtt ccttcagctc cactggaact
2821 acactctcct ctgagtgcca gccatggccc tgccaaggcc catctcgctt gttatctgcc
2881 tgatccctgg gtcccactat cttgcttagc aacccgaggt gggaatcttg gctattcccc
2941 catgtggtgg ggactcaaca ctccccggtg actctgggga ggaggcagca ctaggtgctg
3001 gccttggagc ctgccctgac cttgggaagc tgggcagcgt gggtggagag agactgctca
3061 cacaagcctt tgctctgttt gcagaatgca ccttctgagg cacctccagc tgccccggc
3121 cgggggatgc gaggctcgga gcacccttgc ccggctgtga ttgctgccag gcactgttca
3181 tctcagcttt tctgtccctt tgctcccggc aagcgcttct gctgaaagtt catatctgga
3241 gcctgatgtc ttaacgaata aaggtcccat gctccacccg
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FIGURE 8

(page 1 of 2)

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   1 ccctggggtg cagctgagct agacatggga cggcgagacg cccagctcct ggcagcgctc
  61 ctcgtcctgg ggctatgtgc cctggcgggg agtgagaaac cctgtaagtg aaggagaggg
 121 tctttttatg tgctttcttt atttctctta aagaaaaaaa aaaagcacaa ccataaatta
 181 acttgagagg gggaatggct ataaaggcat ctggcaatgt gtgttgttca catgggattt
 241 gccactgctc aggagggtgg ctccaagaag ggcctccctc ctagggaaag gctgagtgac
 301 ggcaggtgtc agcgggcccc gtgtcgggcc aggagggcat tcccaccaag ggtccttgga
 361 gtcccagagc actcacctct cgcctggatc ttggccttgg gtccatctgt tcaccctcct
 421 ctaggagggt tttgtttttg ttttttttccg agacaggatc tggctttgcc gcccaggcag
 481 gagtgcagtg gtgtgatctt ggctcactgc aacctctgcc tcccaggctc aagtgatcct
 541 cccacctcag ccgcctgagt agctgaaacc acagttgtgg accatcatgc ccggccaatt
 601 ttttttttttg tattgtttgt agagatgggg tttcgacatg ttgcccagga tggtcttgaa
 661 ctcctgagct caagcaatct gcccgcctcg gcttcctaaa gtgctgggat tataggtatg
 721 agccaccatg cctggctttt tttttttttt ccttttaaac taatataaca atttcagcaa
 781 agccctatcg gcttctcagg aggaaaccgc attgcttaaa tatgggcaag ataagacttt
 841 gtgtttctct atgtggcaac aagacagtag aggcatcccc tagaacctct gagagaagga
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FIGURE 8

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FIGURE 9

(page 1 of 2)

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FIGURE 9

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/12891

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 38/00, 38/16
US CL : 514/2, 12
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/2, 12; 435/69.1, 91, 172.3, 320.1, 235.1; 536/27, 23.5; 530/300; 935/9, 10, 23

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,E	US 6,221,840 B1 (PODOLSKY et al) 24 April 2001 (24.04.2001), abstract, column 1, lines 25-38, column 15, lines 33-47, column 16, lines 1-5, column 27 lines14-35, column 28, lines 13-34.	1-6, 34-38, 42
X	US 6,063,755 A (PODOLSKY et al) 16 May 2000 (16.05.2000), abstract, column 1, lines 29-33, column 3, lines 61-67, column 9, lines 31-34, column 10, lines 1-3.	1-16, 34-38, 42
A	MODLIN et al. Trefoil Peptides: Mitogens, Motogens, or Mirages? J. Clin. Gastroenterol. 1997, Vol.25 (Suppl. 1), pages S94-S100.	1-7, 10-16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
30 July 2002 (30.07.2002)

Date of mailing of the international search report
11 SEP 2002

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Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/12891

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-55 (in-part)

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

PCT/US02/12891

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

1. This International Preliminary Examining Authority has found greater than 1 invention claimed in the International Application covered by the claims indicated below:

This application contains more than one invention or group of inventions wherein the inventions or group of inventions consists of a method and a product:

Group I, claim(s) 1-55, drawn to methods of treatment by trefoil peptide and a second therapeutic and the composition for such treatment.

However, the first invention claims a method of treatment requiring a trefoil peptide and subsequently claims three peptides of similar function but are structurally different for use in the treatment scheme. One or more of the peptides is/are known in the art (i.e. intestinal trefoil factors) (U.S. Patent No. 6,063,755) and therefore lack a special technical feature. Applicant must elect one peptide of the three. Additionally, the first invention claims a second therapeutic for use in conjunction with one of the structurally different peptides, however, the applicant claims six different classes of compounds to represent the second therapeutic wherein the classes are further divided into subgroups of therapeutics. The applicant must elect one representative for the second therapeutic. Furthermore, the first invention claims formulations for the peptide and the second therapeutic as being the same or different. The applicant needs to elect one formulation as same or different one from the other. For explanation of possible combinations see below:

1. Trefoil peptides: [A] spasmolytic polypeptide; [B] pS2; [C] intestinal trefoil factor. Applicant will receive search for [A] or Applicant must pay additional for either or both [B] and [C].

2. Second Therapeutic:
   a. anti-inflammatory;
   b. Antibacterial agent; (i) penicillin, (ii) cephalosporin, (iii) tetracycline, (iv) aminoglycoside, or (v) povidoneiodine.
   c. anti-fungal agent; (i) nysttin or (ii) Amphotericin B.
   d. anti-viral agent;
   e. analgesic; (i) lidocaine or (ii) benzocaine.
   f. steroid; (i) triamcinolone or (ii) hydrocortisone.

3. As to each of (a) to (f), Applicant needs to elect from (a); after first member of group additional fees for each member are required.

3. Formulation:
   a. same formulation
   b. different formulation

As demonstrated by the itemization above, there are 78 possible combinations of methods. Additional fees are required for searches beyond the first member or each group above. If additional members are not chosen and the required fees paid for the additional members, the first member of each group only will be searched.

Continuation of B. FIELDS SEARCHED Item 3:

JCID: <WO_____02085402A1_I_>

INTERNATIONAL SEARCH REPORT

PCT/US02/12891

STN, SCISEARCH, BIOSIS, WEST, MEDLINE, TREFOIL, INTESTINAL, PEPTIDE, FACTOR, INFLAMMATORY, BACTERIAL, FUNGAL, ANTI, VIRAL, ANALGESIC, STEROID, LESION, ALIMENTARY, INFLAMMATION